Psychotraumatology

Key Papers and Core Concepts in Post-Traumatic Stress

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Biological Approaches to the Diagnosis and Treatment of Post-Traumatic Stress Disorder

MATTHEW J. FRIEDMAN

Biological approaches to the diagnosis and treatment of PTSD are receiving increasing attention from scientists and clinicians. Research findings appear to suggest that patients with PTSD display marked abnormalities in sympathetic nervous system arousal, in hypothalamic-pituitary-adrenocortical function, in the endogenous opioid system, and in the physiology of sleep and dreaming. Such results enable us to expand our theoretical understanding of PTSD from a purely psychological context to a bio-psycho-social model in which many different factors contribute to the pathology of PTSD.

In this chapter I will review current advances in biological research on PTSD, and I will demonstrate how a biological perspective may complement psychological diagnostic techniques to achieve greater precision in identifying PTSD. This is especially pertinent in distinguishing PTSD from either major depressive disorder (MDD) or panic disorder (PD), because PTSD exhibits many of the same symptoms as each of these other psychiatric illnesses.

I will also review current knowledge on pharmacotherapy of PTSD in the context of our present understanding of the unique pathophysiology of

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this disorder. Neurobiological models also suggest why patients with PTSD may be particularly susceptible to alcohol and other chemical abuse/dependency. Such theoretical considerations will be reviewed in the context of treatment implications of patients with the dual diagnosis of PTSD and chemical abuse/dependency.

HISTORICAL PERSPECTIVE

Abraham Kardiner's research on World War I veterans during the 1940s has proved to be highly influential in stimulating modern biological approaches to PTSD (Kardiner, 1941; Kardiner & Spiegel, 1947). Theorizing from the psychological perspective of stress and adaptation, Kardiner stated that (what is now called) PTSD was a "physioneurosis" in which the patient's adaptive capacity was "smashed." He believed that PTSD was both a psychological and a physiological disorder with its own unique pathophysiology. To underscore this biological orientation Kardiner labeled the dissociative episodes now called flashbacks as an "epileptic symptom complex," implying that they were caused by some disorder of brain function.

A few years later Cohen and others investigated neurocirculatory asthenia (NCA) on a clinical population consisting mostly of combat veterans (Cohen et al., 1948; Cohen & White, 1950). Placing their work in a historical context of physiological and medical research on combat survivors dating back to the Civil War (Beard, 1869; DaCosta, 1871; Hartshorne, 1864; Lewis, 1917; Wood, 1941), they recognized that NCA had previously had many other names, including soldier's heart, anxiety neurosis, nervous exhaustion, DaCosta's syndrome, irritable heart, and effort syndrome. Cohen and associates elegantly showed that combat veterans with NCA had many abnormalities that could be readily detected when they were asked to perform muscular work on a treadmill. Patients with NCA (a) could not work as long as controls, (b) had a metabolic defect evidenced by less efficient oxygen consumption and higher blood lactate concentration, (c) had reduced pulmonary ventilatory efficiency, (d) had excessively high pulse rates during work, and (e) showed abnormal reactivity to painful stimuli.

Because most of their subjects were World War II veterans, Cohen and associates speculated about the possible impact of military experience on their experimental observations. They noted that many of their subjects had been in good health before the onset of NCA. They also noted that the vast majority of their subjects "blamed the army for their difficulties" and that "a high percentage of patients . . . reported a harrowing experience in combat" (Cohen et al., 1948, p. 278). Other subjects suggested that family violence, death, and illness preceded the onset of NCA. Cohen et al. never went beyond such preliminary observations to explore the possibility that exposure to trauma was the common denominator for many of their subjects.

They were apparently unaware of Kardiner's work on the impact of combat trauma and concluded that the cause of NCA was "unknown."

These important early investigations by Cohen et al. have recently been rediscovered by researchers studying the pathophysiology of panic disorder. Perhaps Cohen et al.'s, assertion that NCA had no known etiology accounts for the fact that their work is seen as a pioneering effort in the field of panic disorder rather than PTSD. Recent findings with PTSD patients by biologically oriented investigators, however, suggest that the work of Cohen et al. is also relevant to PTSD. With regard to cardiovascular function, Israeli combat veterans with PTSD exhibit low effort tolerance and decreased cardiac reserve in comparison with controls (Shalev et al., 1990). Burn patients with PTSD have significantly lower pain thresholds than burn patients without PTSD (Perry et al., 1987). Reports of a possible link between chronic pain and PTSD (Benedikt & Kolb, 1986; Rapaport, 1987) are also consistent with these observations of hyperalgesia among PTSD patients. Finally, reports of higher rates of somatic complaints among Israeli combat veterans with PTSD (Solomon & Mikulincer, 1987) update similar observations by Cohen et al. (1948) among World War II veterans with NCA.

These clinical observations indicate how exposure to trauma may alter the body's normal physiology and health. At face value, such findings suggest that the port of entry into our health care system for some PTSD patients may be via cardiac, pain, or other medical clinics. At another level, of course, such findings suggest that PTSD is associated with a number of biological alterations that may be expressed somatically as well as psychiatrically.

BIOLOGICAL ALTERATIONS ASSOCIATED WITH PTSD

Sympathetic Nervous System

Dysregulation of the sympathetic nervous system has been demonstrated by monitoring the psychophysiological response of combat veterans upon exposure to traumagenic stimuli, by measuring urinary catecholamine levels, and by determination of peripheral alpha-2 and beta-adrenergic receptor binding in patients with PTSD (Table 11.1).

A thorough discussion of this research is beyond the scope of this chapter, and the reader is referred to Kolb's (1987) elegant recent review for more information. Briefly, uncontrolled findings on combat veterans with PTSD include increased muscle tension (Gillespie, 1942) and increased heart rate, respiration rate, and EEG alpha rhythm (Dobbs & Wilson, 1961). A major methodological breakthrough occurred when Blanchard et al. (1982) recognized that the hallmark of PTSD is a conditioned emotional response to meaningful stimuli that trigger thoughts, memories, and feel-

Table 11.1 Biological Alterations Associated with PTSD

1. Sympathetic nervous system hyperarousal
   a. Elevated baseline sympathetic physiological indices
   b. Sympathetic psychophysiological response upon exposure to traumagenic stimuli
   c. Elevated urinary catecholamine levels
   d. Reduced platelet MAO activity
   e. Down-regulation of adrenergic receptors
2. Hypofunction of hypothalamic-pituitary-adrenocortical axis
   a. Decreased urinary cortisol levels
   b. HPA suppression following dexamethasone
   c. Unique elevation of urinary catecholamine/cortisol ratio
3. Abnormalities of the endogenous spioid system
   a. Stress induced analgesia by traumagenic stimuli
   b. General lowering of the pain threshold at rest
4. Sleep abnormalities
   a. Initiating and maintaining sleep: increased sleep latency, decreased total sleep time, decreased sleep efficiency, increased number of awakenings, increased body movements
   b. Sleep architecture: changes are controversial
   c. Traumatic nightmares are unique

ings uniquely associated to the trauma itself. They have shown that at baseline, Vietnam combat veterans with PTSD exhibit higher heart rate, systolic blood pressure, and forehead EMG than controls. More importantly, PTSD patients exhibit dramatic physiological arousal after exposure to an audiotape of combat sounds played at gradually increasing volume levels. The heart rate, systolic blood pressure, and EMG responses of PTSD patients were so much greater than those of controls that blind raters correctly classified them 95.5% of the time. Similar results have been obtained in other laboratories (Brende, 1982; Malloy et al., 1983). Psychophysiological arousal in Vietnam combat veterans with PTSD has also been elicited by other traumagenic stimuli (Pitman et al., 1987, 1988).

One would predict that sympathetic psychophysiological hyperreactivity would be associated with elevated catecholamine levels. Indeed, elevated urinary norepinephrine (Kosten et al., 1987; Mason et al., 1985) and epinephrine levels (Kosten & Krystal, 1988; Kosten et al., 1988) have been found in Vietnam combat veterans with PTSD. Kosten et al. (1987) reported that 24-hour urinary norepinephrine and epinephrine levels in PTSD patients were significantly higher than those of normals and of patients with panic disorder, major depressive disorder, undifferentiated schizophrenia, paranoid schizophrenia, and manic-type bipolar disorders. Mason and associates (1985) had previously reported that PTSD patients have a higher urinary norepinephrine/cortisol ratio. This ratio results both from elevated urinary norepinephrine levels and from the reduced urinary cortisol levels that are uniquely found in PTSD patients (Mason et al., 1986; see below).

Whereas elevated catecholamine levels may be biochemical markers for the sympathetic dysregulation association with PTSD, they may also reflect another abnormality, reduced monoamine oxidase (MAO) activity in combat veterans with PTSD. MAO is a major degradative enzyme in catecholamine metabolism, so reduced MAO activity could lead to higher systemic norepinephrine and epinephrine levels. In this regard, Davidson and associates (1985) reported a significant reduction in platelet MAO activity among combat veterans with PTSD. As discussed by Kosten and Krystal (1988), interpretations of these findings must be cautious because of the simultaneous occurrence of depression and/or alcoholism in many of these patients.

Finally, three studies on adrenergic receptor binding are consistent with all of the above results, suggesting that PTSD is associated with higher sympathetic nervous function. One would predict that increased adrenergic synaptic activity should desensitize or down-regulate adrenergic receptors. Consistent with this prediction, Perry et al. (1987) observed fewer total platelet alpha-2 receptor binding sites in 12 Vietnam veterans with PTSD as compared with 13 age-matched controls. In addition to down-regulation, Perry et al. (1988) showed in a more recent report that the alpha-2 receptor complex is uncoupled and therefore functions less efficiently in the platelets of patients with PTSD. Similarly, Lerer and associates (1987) studied beta-adrenergic receptor binding in both intact lymphocytes and platelet membrane preparations. They found that PTSD patients exhibited abnormally low beta-adrenergic receptor-mediated cAMP signal transduction.

Hypothalamic-Pituitary-Adrenocortical (HPA) Axis

Turning from the sympathetic nervous system to the hypothalamic-pituitary-adrenocortical (HPA) axis, data on urinary cortisol levels and the dexamethasone suppression test (DST) suggest that hypofunction of the HPA axis is associated with PTSD. Mason and associates (1986) have shown that 24-hour urinary free-cortisol levels are significantly lower among PTSD patients than in most other psychiatric disorders. Furthermore, normal suppression of the HPA axis by dexamethasone has been shown in PTSD patients (Kudler et al., 1987). Two theoretical explanations have been proposed to explain HPA axis hypofunction in PTSD. Mason et al. (1986) have cited older psychosomatic research suggesting that denial and psychological defenses can exert a strong suppressive effect upon urinary corticosteroid levels. A more parsimonious hypothesis postulates that biological rather than psychological mechanisms may account for HPA axis hypofunction. This argument is based on the previously discussed possibility that PTSD is associated with increased central noradrenergic activity. Because norepinephrine inhibits the release of corticotropin-releasing hormone (CRH; Price et al., 1986), the postulated increased central sympathetic activity of PTSD would be expected to inhibit the entire HPA system.

Endogenous Opioid System

Kosten and Krystal (1988) have suggested that adrenergic inhibition of CRH may also account for a disturbance in the endogenous opioid system associated with PTSD. CRH promotes release of ACTH from the pituitary; ACTH is coreleased with beta endorphin, which influences the activity level of the endogenous opioid system. Kosten and Krystal postulate that inhibition of CRH by excessive sympathetic arousal therefore will also produce an endogenous opioid deficiency in patients with PTSD. This prediction is consistent with previously mentioned clinical reports of lowered pain thresholds in PTSD patients (Perry et al., 1987) and of a possible link between chronic pain and PTSD (Benedikt & Kolb, 1986; Rapaport, 1987). Finally, Pitman and associates (1990) have recently shown that exposing Vietnam veterans with PTSD to combat scenes from the movie *Platoon* produces a naloxone-reversible 30% decrease in pain responses. This important finding of stress-induced analgesia suggests not only that PTSD is associated with dysregulation of the endogenous opioid system but also that a possible baseline opioid deficiency might be dramatically reversed when PTSD patients are exposed to traumagenic stimuli.

Sleep and Dreaming

Abnormalities in sleep and dreaming also appear to be associated with PTSD. Patients often have difficulty initiating and maintaining sleep (Table 11.1). In addition, several studies show marked disruption of sleep architecture in PTSD exemplified by increased stage 1, increased stage 2, decreased delta sleep, decreased REM latency, and increased total REM percentage (Kramer & Kinney, 1985, 1988; Kramer et al., 1982; Lavie et al., 1979; Schlossberg & Benjamin, 1978). These results are controversial, however, especially with regard to REM latency and total REM percent (Greenberg et al., 1972; Van Kammen et al., 1987). An excellent review by Ross et al. (1989) clarifies methodological problems and substantive contradictions on the emerging literature on sleep in PTSD.

In addition to alterations in physiological sleep, disturbed dreaming is a prominent abnormality in chronic PTSD (Kramer, 1979; van der Kolk et al., 1984). Traumatic nightmares may arise out of REM or non-REM (NREM) sleep (van der Kolk et al., 1984). As noted earlier (Friedman, 1981), these nightmares appear to be unique to PTSD because they are neither REM dream anxiety attacks nor NREM night terror/nightmares (Kramer, 1979).

Ross et al. (1989), however, suggest that PTSD nightmares may actually be a newly identified phenomenon called REM sleep without atonia. The signifying characteristic of the PTSD nightmare is an "instant replay" of the traumatic event, often accompanied by nocturnal muscle movements that are consonant with the events of the nightmare.

Neurobiological Models of PTSD

A number of models have been proposed to integrate the biological abnormalities and clinical symptoms associated with PTSD. Discussion of these models is beyond the scope of this article and the reader is referred to recent reviews for more details (Friedman, 1988; Kolb, 1987; Kosten & Krystal, 1988; van der Kolk, 1987; van der Kolk et al., 1985). All of these models presuppose hyperarousal of the central noradrenergic system and focus especially on the locus coeruleus because it is instrumental in the neurobiology of arousal and panic.

Kolb (1987) has postulated that the excessive and prolonged high-intensity stimulation from traumatic exposure produces cortical neuronal and synaptic changes in patients with chronic PTSD. He hypothesizes that the conditioned fear response of PTSD therefore is associated with alteration in brain functions that control aggressive expression and the sleep-dream cycle. This model accounts for the dramatic psychophysiological response in PTSD patients following exposure to traumagenic stimuli.

Van der Kolk and associates (1985) have proposed that the animal model of learned helplessness in response to inescapable shock may be directly applicable to PTSD. They hypothesize that long-term potentiation of locus coeruleus pathways to the hippocampus and amygdala may produce the hyperarousal, traumatic nightmares, and flashbacks that characterize PTSD. Such a theory also suggests that fluctuations in endogenous opioid levels will affect the response to traumagenic stimuli, because the locus coeruleus is inhibited by opioids. The inescapable shock theory offers a neurobiological rationale for stress-induced analgesia and for the "action junkie" behavior that is sometimes considered secondary to PTSD. It also has implications for opiate addiction that will be discussed later.

Van der Kolk (1987) and Friedman (1988) have independently suggested that kindling is a neurobiological model that may be as applicable to PTSD as it is to a cocaine model of psychosis (Post & Kopanda, 1976). Kindling is a process by which neuroanatomic structures, especially those in the limbic system, become increasingly sensitized following repeated exposure to electrical stimulation or cocaine-like drugs. Kindling can lead progressively to profound neurophysiological abnormalities such as grand mal seizures or to the progressive development of aberrant behavior. According to this model, chronic central sympathetic arousal in PTSD, mediated by the locus coeruleus, kindles limbic nuclei, thereby producing a stable neurobiological abnormality. Kindling would explain the stability of PTSD—if untreated, it can persist for decades (Archibald & Tuddenham, 1965). This model also suggests that an antikindling drug such as carbamazepine might be pharmacologically efficacious in PTSD.

BIOLOGICAL APPROACHES TO DIAGNOSIS

Among biological diagnostic techniques that have been tested are psychophysiological assessment, the dexamethasone suppression test (DST), the sleep EEG, sodium lactate infusion, and the sodium amytal interview. In this section I will review the applicability of these diagnostic techniques to PTSD and evaluate their potential for distinguishing PTSD from major depressive disorder (MDD) and panic disorder (PD; see Table 11.2).

Psychophysiological Assessment

Currently the best and most specific biological diagnostic test for PTSD is psychophysiological assessment. This diagnostic technique is based on the fact that traumagenic stimuli elicit sympathetic hyperarousal, as discussed earlier (Blanchard et al., 1982; Kolb, 1987; Malloy et al., 1983; Pitman et al.,

Table 11.2 Biological Diagnostic Tests for PTSD

	PTSD	MDD	PD
I. Psychophysiological responses to traumagenic stimuli			
Sympathetic arousal	+	−	−
Stress-induced analgesia	+	−	−
II. HPA axis abnormalities			
DST	−	+	−
Urinary cortisol	↓	↑	?
III. Sleep EEG abnormalities			
Initiating and maintaining sleep	↓	↓	↓
Movements during sleep	↑	0	↑
Stage 1 and stage 2	↑	0	0
Delta	↓	↓	0
REM	↑/↓	↑/0	0
REM latency	↑/↓	↓	0
IV. Sodium lactate infusion			
Panic attacks	?	−	+
Flashbacks	?	−	−
V. Sodium amytal interview	+	−	−

Note: + = proven diagnostic value, − = no apparent diagnostic value, ? = unknown diagnostic value, ↓ = reduced, 0 = no change, ↑ = increased.

1987). This technique is both sensitive and powerful when one uses a general stimulus such as an audiotape of combat sounds or a visual excerpt from a movie such as *Platoon*. It is even more discriminatory when the provocative stimulus is an individualized autobiographical traumatic anecdote (Pitman et al., 1987).

Exposure to traumagenic stimuli may also have practical applicability as a clinical paradigm for testing biological markers other than sympathetic arousal, such as HPA axis function or stress-induced analgesia. In the development of standard diagnostic approaches, however, biological markers in PTSD patients should be assessed both at baseline and immediately after provocation by traumagenic stimuli.

Dexamethasone Suppression Test

The dexamethasone suppression test (DST; Carroll et al., 1981) has enjoyed wide use in diagnosing major depressive disorder (MDD). It is based on the fact that MDD is a disorder that is associated with hyperfunctioning of the HPA system. For this reason, dexamethasone, which normally suppresses HPA activity, cannot do so in patients with MDD. Depressed patients therefore are often "nonsuppressors" when challenged by the DST. In an earlier article (Friedman, 1988), I suggested that DST might be useful for distinguishing PTSD from MDD. After all, PTSD appears to be associated with hypofunctioning of the HPA system, whereas MDD seems to be just the opposite. Therefore I predicted that PTSD patients would have a normal DST; they would be suppressors, whereas patients with MDD would be nonsuppressors. The work of Kudler et al. (1987) was consistent with this prediction. Patients with PTSD alone were suppressors, whereas those with *both* PTSD and MDD were nonsuppressors following a dexamethasone challenge. Subsequently, Halbreich and associates (1988) confused the issue when they compared DST responses of patients with MDD alone with a second group that had *both* MDD and PTSD. This time the MDD + PTSD patients were suppressors, in contrast to MDD-alone patients, who were nonsuppressors. These results indicate that when PTSD and MDD coexist in the same patients, PTSD-induced HPA hypofunction may neutralize MDD-induced HPA hyperfunction. From the practical standpoint of clinical diagnosis, Halbreich et al.'s results have two implications. First of all, they suggest that the DST may have limited value in distinguishing PTSD from MDD. Second, and more importantly, these results suggest that when both PTSD and MDD occur simultaneously, each may alter the biological expression of the other.

Sleep EEG

Investigations on the sleep EEG of depressed patients have shown that MDD is reliably associated with alterations in sleep architecture. Specifically, depressed patients exhibit reduced REM latency and reduced delta sleep, and the duration of the first REM period is prolonged in MDD (Akiskal, 1983; Dube et al., 1986; Kupfer & Thase, 1983; Ross et al., 1988). As discussed earlier and shown in Table 11.2, it would appear that there might be enough differences between MDD and PTSD to predict that the sleep EEG will play an important role in the differential diagnosis of MDD versus PTSD. There is a problem with such a prediction. First of all, if (as suggested above with regard to the DST) the simultaneous occurrence of MDD and PTSD alters the unique biological expression of each disorder, then the sleep EEG may also lose its specificity in patients who have both depression and PTSD. Indeed, such a possibility may explain some controversies in the literature and especially why some investigations have observed sleep EEG findings in PTSD patients that look more like expected results in depression (Greenberg et al., 1972; Kauffman et al., 1987, Van Kammen et al., 1987).

To summarize, the potential usefulness of the sleep EEG in distinguishing MDD from PTSD has not been adequately tested. Perhaps it will be more useful for future studies to focus primarily on the length of the first REM period rather than the total nocturnal percentage of REM sleep (Ross et al., 1988). Undoubtedly future studies will have to state quite explicitly whether their clinical populations meet diagnostic criteria for MDD, PTSD, or both.

The sleep EEG, however, should easily distinguish PTSD from PD. There is apparently no disturbance of the sleep architecture in PD, although panic patients do exhibit difficulty initiating and maintaining sleep and, like PTSD patients, show increased body movements while asleep (Dube et al., 1986; Hauri et al., 1989).

Sodium Lactate Infusion

One of the most definitive diagnostic tests for PD is the sodium lactate infusion. Pitts and McClure's (1967) original observation that intravenous administration of sodium lactate can precipitate panic attacks in patients with PD has been replicated by many investigators. PD and PTSD share many characteristics in common. Both disorders may be associated with locus coeruleus dysregulation, because both exhibit sympathetic hyperarousal and sudden surges of anxiety. In addition, PTSD flashbacks may meet DSM-III-R diagnostic criteria for panic attacks (Mellman & Davis, 1985). For these reasons, it would be very interesting to learn whether sodium lactate can induce PTSD symptoms as it can panic attacks. To date, the only report on this subject is quite confusing (Rainey et al., 1987). Although the authors report that lactate infusion precipitated flashbacks in all seven subjects, only one such "flashback" was a reexperiencing of combat trauma. All other "flashbacks" occurred in a hospital setting more comparable to the laboratory experimental situation than to the combat trauma responsible for the later development of PTSD. Furthermore, because all patients met DSM-III-R criteria for PD as well as PTSD, their susceptibility to sodium lactate may differ considerably from the responsivity of PTSD patients who do not simultaneously meet DSM-III-R criteria for PD. In my opinion, it is still unclear whether PTSD patients will respond to a lactate infusion. It is an important question that needs to be investigated systematically. Furthermore, other established provocative tests for PD, such as carbon dioxide inhalation (Fryer et al., 1987) and yohimbine challenge (Charney et al., 1987), also need to be explored with PTSD patients.

Sodium Amytal Interview

PTSD has revived interest in narcosynthetic exploration of repressed traumatic experiences or dissociative episodes triggered by traumagenic stimuli (Kolb, 1985). After decades of neglect, the sodium amytal interview is proving to be a useful clinical tool for identifying catastrophic stressors that are too terrifying for discussion in the normal state of consciousness. Clearly this diagnostic technique has a unique applicability to PTSD, in contrast to MDD or PD.

As defined by Kolb (1985), narcosynthesis is drug-induced recall of repressed material through an abreactive experience. Through this procedure, repressed material becomes consciously available for later integration and synthesis by the personality. The amytal interview is not an end in itself but rather a technique for exposing material through narcosynthetic abreaction that must be worked through in subsequent psychotherapy. Candidates for this approach are individuals who have complete or partial amnesia for recurrent episodes of abnormal behavior in which they may become aggressively threatening or violent. Such dissociative episodes are often precipitated by traumagenic stimuli and seem more likely to occur if the patient has been drinking beforehand.

The key to the narcosynthetic approach is videotaping the entire session. After full recovery of consciousness, the patient reviews the entire tape with his or her therapist so that recently repressed information can be incorporated into ongoing psychotherapy. The reader is referred to Kolb (1985) for further details on indications, contraindications, and the specific technique for the amytal interview.

Differential Diagnosis: PTSD, MDD, and PD

Because PTSD shares many symptoms in common with MDD and PD, it is useful to review current knowledge on biological diagnostic tests to clarify their distinguishing features as well as their similarities. PTSD and MDD are both associated with symptoms such as dysphoria, guilt, grief, anhedonia, irritability, social withdrawal, and insomnia. In addition, both disorders respond to some of the same medications (shown in Table 11.3 and discussed below). Likewise, PTSD and PD are anxiety disorders marked by sympathet-

Table 11.3 Response to Medication: PTSD, MDD, and PD

	PTSD	MDD	PD
Tricyclic antidepressants	+	+	+
MAO inhibitors	+	+	+
Carbamazepine	(+)	?	0
Lithium	(+)	+	0
Benzodiazepines	(+)	−	+
Alprazolom	(+)	+	+
Propranolol	(+)	−	+
Clonidine	(+)	−	(+)
Neuroleptics	±	±	0

Note: + = proven therapeutic efficacy, (+) = promising uncontrolled trials, 0 = ineffective, − = worsens condition.

ic hyperarousal, an association with depressive symptoms, panic attacks, responsivity to similar medications (see Table 11.3), and a hypothesized locus coeruleus dysregulation.

In my opinion, the observations tabulated in Table 11.3 are consistent with the hypothesis that each of these three disorders has a unique biological profile that can be detected by appropriate diagnostic techniques. It is necessary to sound two cautionary notes about the data summarized in the table. First of all, it is premature to be dogmatic about any of these findings on PTSD, given the general paucity of studies. Second, because DST results (Halbreich et al., 1988) suggest that when PTSD and MDD occur simultaneously, each may alter the biological expression of the other, further research is needed in which PTSD, MDD, and PD are compared systematically in the same experimental protocol.

To summarize, as shown in Table 11.3, the psychophysiological response to traumagenic stimuli is the hallmark of PTSD with regard to hyperarousal of the sympathetic nervous system and as manifested by the endogenous opioid mobilization associated with stress-induced analgesia. Although PD is also marked by hyperarousal of the adrenergic system, panic attacks are spontaneous events (rather than a response to emotionally charged stimuli) and are essentially a physiological event devoid of the psychological meaning associated with PTSD episodes. The distinctive HPA hyperactivity of MDD contrasts with HPA hypoactivity in PTSD. For practical purposes, because the DST is normal in PTSD and urinary cortisol levels are not routinely obtained, testing the HPA axis may have limited value in the clinical diagnosis of PTSD. All three disorders show sleep EEG abnormalities, and all three exhibit difficulties initiating and maintaining sleep. Only PTSD and MDD appear to exhibit alterations in the sleep architecture, as discussed previously. The sodium lactate infusion has not been adequately tested in PTSD, as also noted above. Finally, the sodium amytal interview is uniquely applicable to PTSD.

CLINICAL PSYCHOPHARMACOLOGY

From our current understanding it appears that any drug that can reduce excessive noradrenergic activity will be beneficial in PTSD. This might be accomplished by direct antagonism of sympathetic nervous system arousal (propranolol and other beta-adrenergic blocking agents), or by reduction of brain locus coeruleus activity via inhibiting alpha-2 adrenergic receptors (clonidine, tricyclic antidepressants). If PTSD results from limbic kindling (Friedman, 1988; van der Kolk, 1987) an antikindling agent such as carbamazepine might also be effective.

Most of the information on pharmacotherapy comes from open trials and case reports. A number of double-blind investigations are currently in process, and a few preliminary reports have been presented. Given the current paucity of data from controlled clinical trials, it should come as no surprise that prescribing practices may differ widely from one place to another. For example, at one VA hospital 59% of all PTSD patients received tricyclic antidepressants either exclusively (38%) or in combination with other psychotropic agents (Embry & Callahan, 1988). At another VA hospital, 71% of PTSD patients received benzodiazepines either exclusively (36%) or in combination with other drugs (Ciccone et al., 1990).

Tricyclic Antidepressants

Several clinical reports indicate that tricyclic antidepressants (TCAs) may be effective drugs for PTSD. Published observations suggest that TCAs reduce such specific PTSD symptoms as hyperarousal, intrusive recollections, flashbacks, and traumatic nightmares. Although the antidepressant action of TCAs is often useful against depressive symptoms that may be associated with PTSD, the primary therapeutic target symptoms under discussion here are PTSD and not MDD symptoms. Anecdotal reports and open trials using rating scales have generally reported that TCAs reduce DSM-III-R intrusive recollection and hyperarousal symptoms but have little effect on avoidant symptomatology (Blake, 1986; Bohnlein et al., 1985; Burstein, 1982; Embry & Callahan, 1988; Falcon et al., 1985; Friedman, 1981, 1988; Marshall, 1975; van der Kolk, 1987). Similar results have been obtained with different traumatized cohorts such as accident victims, burn patients, combat veterans, and Cambodian concentration camp survivors. Davidson et al. (1988) conducted an 8-week double-blind randomized trial of amitriptyline versus placebo. They found that amitriptyline was most effective in patients who had depressive symptoms and that this drug did not appear to have specific effects on either intrusive or avoidant PTSD symptoms. In contrast, Frank et al. (1988), conducting a randomized double-blind trial of imipramine, phenelzine (an MAO inhibitor), and placebo observed moderate reduction in both intrusive ad avoidant PTSD symptoms with greater effects on intrusive symptoms. Their observation that improvement in PTSD symptoms was independent of the antidepressant response to imipramine conflicts directly with Davidson et al.'s conclusions. Clearly there is need for additional research, as these results cannot be reconciled.

MAO Inhibitors

MAO inhibitors (MAOIs) have received attention since Hogben and Cornfield (1981) reported that they reduced panic, anxiety, insomnia, and intrusive symptoms in 5 combat veterans with PTSD. MAOIs are attractive agents to consider because of their proven efficacy against the sympathetic dysregulation of panic disorder, their antidepressant activity, and their inhibition of REM sleep. Phenelzine is the only MAOI that has been studied, and most reports describe open-trial case reports on very few patients (Milanes et al., 1984; Shen & Park, 1983). In two larger studies, Davidson et al. (1987) and Lerer et al. (1987) conducted open trials on 11 and 22 combat veterans, respectively. Both groups observed that phenelzine's primary PTSD effect was on intrusive rather than avoidant symptoms, although reductions in general anxiety and depressive symptoms were also prominent. The only randomized double-blind trial has been Frank et al.'s comparison of imipramine, phenelzine, and placebo discussed above. These investigators reported that phenelzine was even more effective than imipramine against intrusive symptoms; it produced little improvement in avoidant symptoms. The therapeutic efficacy of MAOIs (like imipramine) in this study was completely independent of its antidepressant effect.

The decision to prescribe phenelzine will have to take into consideration a realistic expectation of patient compliance with regard to dietary restrictions and abstention from alcohol, opiates, and other drugs. Therefore high rates of alcoholism and chemical abuse/dependency in combat veterans with PTSD (Branchy et al., 1984; Keane et al., 1988) may preclude extensive use of phenelzine, efficacy notwithstanding.

Carbamazepine

Carbamazepine is an anticonvulsant that was first introduced into psychiatry by Post and Kopanda (1976), who suggested that it be prescribed in lithium-refractory bipolar affective disorder. They based this suggestion on a kindling model of endogenous psychosis.

As noted above, kindling is a neurobiological model that may also be applicable to PTSD (Friedman, 1988; van der Kolk, 1987). For this reason, two investigations have monitored the efficacy of carbamazepine in 10 PTSD patients. Seven patients showed marked reductions in intensity and frequency of the intrusive or "reexperiencing" symptoms of PTSD, such as recurrent nightmares, flashbacks, and intrusive recollections (Lipper et al., 1986). A second open-trial study by Wolf et al. (1988) showed alleviation of impulsivity, violent behavior, and angry outbursts in 10 Vietnam combat veterans with PTSD. Because there has been speculation that complex partial seizures may cause a syndrome similar to PTSD (Greenstein et al., 1986; Stewart & Bartucci, 1986), Wolf et al.'s results are especially notable as all of their carbamazepine patients had normal EEGs and had no symptoms of temporal lobe epilepsy.

Finally, it should be noted that despite the many similarities between PTSD and PD with respect to sympathetic hyperarousal, kindling may not be an appropriate model for PD. Uhde et al. (1988) recently reported on a 3-week double-blind trial of carbamazepine versus placebo in 14 patients with PD. In contrast to its therapeutic value in PTSD, carbamazepine was not effective in PD.

Propranolol

Propranolol is an adrenergic beta-blocker that has documented efficacy in anxiety (Suzman, 1971; Tanna et al., 1977; Tyrer & Lader, 1974) and in panic disorder (Ravaris et al., 1986). As noted above, it is an attractive drug to consider because it would be expected to antagonize the peripheral and (probably the) central sympathetic hyperarousal associated with PTSD. Another advantage of propranolol is that it is a nonbenzodiazepine anxiolytic that can be prescribed without fear of fostering addiction or chemical abuse/dependence in susceptible PTSD patients. In an open trial of propranolol with 14 Vietnam veterans who received 120–160 mg daily for 6 months, most patients reported improvement with specific reductions in nightmares, intrusive recollections, hypervigilence, insomnia, startle responses, and angry outbursts (Kolb et al., 1984). A controlled trial of up to 2.5 mg/kg/day propranolol in 11 sexually or physically abused children with acute PTSD (Famularo et al., 1988) demonstrated significant reduction of intrusive and arousal symptoms. When placebo was substituted for propranolol, the children's symptoms returned to predrug intensity.

Clonidine

Clonidine is an alpha-2 adrenergic agonist currently used in hypertension and opiate withdrawal. It reduces central adrenergic activity by reducing locus coeruleus activity. For that reason it holds out promise as an effective antidote to the adrenergic hyperactivity associated with anxiety disorders. The only information on clonidine in PTSD comes from an open trial with 9 Vietnam veterans who received a daily dose of 0.2–0.4 mg (Kolb et al., 1984). Eight patients had a favorable response marked by lessened explosiveness, reduced nightmares, improved sleep, lessened startle, reduced intrusive thinking, and less hyperalertness. As with propranolol, the authors were careful not to overstate their findings and urged others to conduct systematic controlled trials of both propranolol and clonidine to establish their usefulness in PTSD.

Benzodiazepines

Benzodiazepines are potent anxiolytics that have been prescribed widely for PTSD despite their lack of proven efficacy in controlled trials. Use of benzodiazepines in PTSD, of course, carries with it the risk of addiction and chemical abuse/dependency in susceptible patients (Friedman, 1981, 1988; van der Kolk, 1987). Practical clinical concerns about addiction notwithstanding, the kindling model of PTSD indicates that there may be a neurobiological rationale for prescribing these drugs. Several studies have shown that benzodiazepine receptor binding is increased significantly during the development of limbic kindling (McNamara et al., 1985; Morita et al., 1985; Tietz et al., 1985). This suggests that benzodiazepines and other GABA agonists or synergists might be particularly efficacious in PTSD.

Alprazolam

Alprazolam is a triazolo-benzodiazepine that apparently differs from other benzodiazepines because of its demonstrated antipanic and antidepressant properties (Feighner et al., 1983; Sheehan, 1982). It is currently used widely in PTSD, although there presently are no double-blind studies demonstrating its efficacy. In addition to concerns about addiction and dependence (mentioned previously with regard to all benzodiazepines), alprazolam's pharmacokinetic properties have raised additional concerns. Specifically, its short half-life makes the risk of rebound anxiety and serious withdrawal symptoms greater for alprazolam than for other benzodiazepines that are eliminated more slowly (Higgitt et al., 1985; Noyes et al., 1985).

Lithium

Lithium has been suggested as an effective treatment for PTSD even in patients with no personal or family history of bipolar or cyclothymic illness (Kitchner & Greenstein, 1985; van der Kolk, 1983). Van der Kolk (1987) reported that 14 out of 22 PTSD patients tried on lithium reported markedly diminished autonomic hyperarousal, a decreased tendency to react to stress as if it were a recurrence of their original trauma, and a marked decrease in alcohol intake. Van der Kolk stated that the therapeutic response to lithium in his patients was "clinically indistinguishable" from the aforementioned results with carbamazepine reported by Lipper et al. (1986). As with most other drugs reviewed in this section, there are no systematic double-blind trials of lithium in PTSD.

Neuroleptics

The last drugs to consider are the neuroleptics or antipsychotic agents. When disturbed Vietnam combat veterans first appeared in VA hospitals in the late 1960s and in the 1970s, many of them were prescribed neuroleptics. Psychiatrists impressed by the agitation, bizarre and explosive behavior, rage, anti-authoritarian beliefs merging into paranoia, and brief psychotic episodes that we now call flashbacks often chose a neuroleptic as the drug of first choice. Since that time, we have learned that adrenergic hyperarousal rather than psychotic thinking is the primary target in pharmacotherapy of PTSD. Reduction of DSM-III-R intrusive recollections and arousal symptoms by TCAs, MAOIs, or other drugs is often sufficient to reduce or eliminate psychotic-appearing manifestations of PTSD in most patients. Having learned after almost two decades of misuse and overuse of antipsychotic agents we can now state that neuroleptics have no place in the *routine* treatment of PTSD.

I am not saying that neuroleptics have no value in pharmacotherapy for this disorder, but that they should be used judiciously as a second or third choice following clinical trials of TCAs or other potential first-line drugs. Indications for neuroleptics include aggressive psychotic symptoms (frequently paranoid), overwhelming anger, fragmented ego boundaries, self-destructive behavior, and frequent flashback episodes characterized by visual and auditory hallucinations of traumatic events (Atri & Gilliam, 1988; Friedman, 1981, 1988; Walker, 1982). Mueser and Butler's (1987) report on 5 Vietnam veterans with combat-related PTSD who had auditory hallucinations suggests that there may be a subgroup among PTSD patients for whom neuroleptics are specifically indicated.

Comparative Pharmacotherapy: PTSD, MDD, and PD

Although numerous psychotropic agents have been used for PTSD, there is only one double-blind investigation suggesting that both imipramine and phenelzine have specific efficacy against both intrusive and avoidant symptoms (Frank et al., 1988). A second double-blind trial of amitriptyline versus placebo must be considered equivocal because amitriptyline was most effective in depressed PTSD patients and showed little therapeutic specificity against the symptoms of PTSD (Davidson et al., 1988). With the exception of one study with propranolol in traumatized children, promising claims for the effectiveness of other drugs have not been validated in double-blind clinical trials.

Table 11.3 shows similarities and differences in the psychopharmacological spectrum of action for PTSD, MDD, and PD. All three disorders appear to respond to TCAs, MAOIs, and probably alprazolam. Carbamazepine and lithium, which may be effective in PTSD and MDD, are without potency in PD. Although both drugs are efficacious in bipolar affective disorder, only lithium has proven therapeutic value in MDD. Benzodiazepines and antiadrenergic agents such as propranolol and clonidine (which may be useful in PTSD and PD) can worsen the symptoms of MDD. Finally, neuroleptics (which may be useful in a carefully selected minority of PTSD cases) have limited usefulness in psychotic MDD and are of no value in PD. To summarize, it can be seen from Tables 11.2 and 11.3 that despite considerable overlap in diagnostic abnormalities and responsivity to pharmacological agents, PTSD, MDD, and PD appear each to have unique biological characteristics.

PTSD AND CHEMICAL ABUSE/DEPENDENCY

Most clinicians who treat combat-related PTSD readily acknowledge that therapy is often complicated by coexisting symptoms of alcohol or other chemical abuse/dependency. This clinical impression is confirmed by published reports indicating that 60% to 80% of patients seeking treatment for PTSD have concurrent diagnoses of substance abuse or dependence (Branchy et al., 1984; Keane et al., 1988). Some have argued that such high rates of substance abuse are attributable to the fact that alcohol and other drugs were extremely available to military personnel stationed in Vietnam during the war (Sapol & Roffman, 1969; Wedding, 1987). This cannot explain, however, why veterans with higher levels of combat exposure are more likely to abuse alcohol than those who saw considerably less combat (Keane et al., 1988). Indeed, the latter finding suggests that neurobiological alterations associated with PTSD make affected individuals more susceptible to alcohol and illicit drug use.

Among the biological abnormalities occurring in PTSD, sympathetic nervous system hyperarousal and chronic lowering of endogenous opioid levels are most likely to generate susceptibility to chemical abuse/dependency. Any drug that can suppress central adrenergic activity—such as alcohol, central depressants, marijuana, or opiates—will produce temporary relief in the person suffering from PTSD. Furthermore, the possibility of a chronic opioid deficiency (indicated by lowered pain thresholds) suggests that PTSD patients might successfully ameliorate intolerable symptoms with heroin, methadone, and other opiates. Kosten and Krystal (1988) have elegantly reviewed the biological basis for PTSD symptoms and substance abuse. Arguing theoretically from van der Kolk's inescapable shock model of PTSD, they speculate that "use of ethanol or other drugs such as heroin in acute stress settings of war is an active adaptive style" and that "individuals with a history of recreational substance abuse may be more prone to 'self-medicate'" (Kosten & Krystal, 1988, p. 60). They also point out that during the vicious addiction-withdrawal cycle, the adrenergic arousal associated either with alcohol or opiate withdrawal will trigger a conditioned emotional response associated with PTSD symptoms. In other words, the normal difficulties of treating chemical dependency are multiplied by the complex risk of exacerbating PTSD symptoms. This may be an even greater problem in cases of opiate dependence, because heroin not only dampens adrenergic hyperarousal but may also serve to replenish an endogenous opioid system that has been depleted because of the pathophysiology of PTSD.

Although it is possible that central stimulants effectively relieve the dysphoria of PTSD, especially when depression is also present, one might predict on neurobiological grounds that the incidence of cocaine and amphetamine abuse among PTSD patients will be lower than expected. This is because central stimulants will facilitate sympathetic hyperarousal, thereby exacerbating PTSD symptoms. To my knowledge this has not been studied systematically. In my own clinical experience, however, PTSD patients do not like the heightened emotional state produced by cocaine, amphetamines, and other stimulants. They generally prefer alcohol, marijuana, central depressants, or opiates. Furthermore, cocaine and stimulant users with PTSD are usually also dependent on alcohol, marijuana, opiates, and the like.

When PTSD and chemical abuse/dependency occur simultaneously, they must be treated simultaneously. Rigid adherence to the generic treatment formulas found in many alcohol and drug rehabilitation programs is a prescription for failure. This is because the complex interrelationships between intrapsychic, behavioral, and biological aspects of PTSD and concurrent chemical abuse/dependency demand a comprehensive approach. A detailed description of treatment strategies for patients who carry the dual diagnosis of PTSD and chemical abuse/dependency is beyond the scope of this chapter. Psychopharmacological strategies to be integrated in such an approach may include disulfram (Antabuse) for alcohol dependence and the opiate antagonist naltrexone. Kosten and Krystal (1988) have suggested that the mixed opiate agonist-antagonist buprenorphine may be uniquely suited to "suppress conditioned noradrenergic activation and maintain antagonist self-administration" (p. 62) in PTSD patients undergoing opiate withdrawal. The bottom line, as noted by Stone (1988), is a therapeutic approach that respects both the psychological and neurobiological implications of autopharmacotherapy in patients who suffer from PTSD and chemical abuse/dependency.

CONCLUSION

1. The unique pattern of biological abnormalities associated with PTSD appear to differentiate this disorder from MDD and PD.
2. Provocative laboratory tests that probe PTSD-induced alterations in

noradrenergic activity, the HPA axis, the endogenous opioid system, and the sleep cycle should enable us to achieve greater precision in diagnosing PTSD.

3. Almost every conceivable psychotropic agent has been reported to have efficacy in PTSD. Almost all of these claims are based on clinical anecdotes or open drug trials except for two double-blind investigations on imipramine, phenelzine, and amitriptyline and one controlled study with propranolol.

4. Neurobiological alterations associated with PTSD may make affected individuals more susceptible to alcohol, opiate, and other illicit drug use. The complex interrelationships between intrapsychic, behavioral, and biological aspects of PTSD and concurrent chemical abuse/dependency demand a comprehensive approach to both problems simultaneously.

5. Successful pharmacotherapy for PTSD has generally provided alleviation of DSM-III-R intrusive recollections and arousal symptoms. Avoidant symptoms, impacted grief, guilt, rage, problems with intimacy, and moral pain do not appear to respond to medication. Therefore, it should be understood that drug treatment alone can never alleviate the suffering in PTSD. Pharmacotherapy is primarily useful as an adjunct to psychological (intrapsychic and/or behavioral) treatment of PTSD.

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